RESEARCH ABSTRACT

Title of Project: **Does Smog, Environmental Tobacco Smoke (ETS), or Cat and Dog Allergens Potentiate Airways Disease in Seniors?**

Investigator(s): **M. M. Glovsky, M.D., and Chin Chen Chou, Ph.D., DVM**

Institution: **Huntington Memorial Hospital**

ABSTRACT: In the space below, please provide a descriptive summary of your proposed research project.

The effect of indoor air on respiratory problems is a neglected area; extensive information is available from studies on outdoor air, e.g., smog, pollutants in industrial and natural settings. Understanding factors that contribute to the severity of asthma indoors in a senior population who have lived in a valley which has been subject to outdoor pollution for several decades will also provide data to reduce respiratory diseases in children and young adults, especially if indoor air contains pollutants not previously documented.

Asthma patients report that in certain settings their breathing is affected even though they are in non-smoking areas of restaurants, hotels, or large buildings. Complaints of this type from respiratory patients suggests that studies on indoor air, i.e., dander from animals, ozone/ smog, ETS, need to be conducted utilizing the unique stainless steel challenge chamber located at Huntington Memorial Hospital in Pasadena. Analysis with indoor air for ozone, ETS, and dog allergens will be made.

Chemicals and allergens may potentiate asthma in the indoor environment. By measuring indoor ozone and dog and cat allergens, background levels will be obtained. Challenge in a chamber or indoor setting should provide quantitative lung function changes to correlate the importance of indoor exposures.

M. Richard Glovsky 5/27/93

Signature, Principal Investigator Date

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CENTER FOR INDOOR AIR RESEARCH
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APPLICATION FOR RESEARCH CONTRACT

1. PRINCIPAL INVESTIGATOR. NAME, TITLE, TELEPHONE # AND MAILING ADDRESS.

(A) M. M. Glovsky (B) Medical Director (C) (818)397-3383/795-0982
NAME TITLE TELEPHONE #/ FAX #

(D) Asthma and Allergy Center (E) Huntington Memorial Hospital Asthma Center
DEPARTMENT INSTITUTION

(F) 39 Congress Street, Suite 301, Pasadena (G) California 91105
MAILING ADDRESS STATE/ZIP

2. PROJECT TITLE. Does Smog, Environmental Tobacco Smoke (ETS), or Cat and Dog Allergens Potentiate Airways Disease in Seniors?

3. KEY WORDS. PLEASE PROVIDE THREE (3) KEY WORDS WHICH WILL BE USED AS REFERENCE HEADINGS.
Smog, Allergy, Asthma.

4. INSTITUTION. NAME AND ADDRESS OF INSTITUTION RESPONSIBLE AND ACCOUNTABLE FOR DISPOSITION OF FUNDS AWARDED ON THE BASIS OF THIS APPLICATION:

(A) Huntington Memorial Hospital (B) 100 W. California Boulevard
INSTITUTION STREET ADDRESS

(C) Pasadena (D) CA 91105
CITY STATE/ZIP

5. LOCATION. LIST LOCATION WHERE RESEARCH WILL BE CONDUCTED *IF OTHER THAN INSTITUTION IDENTIFIED IN #4 ABOVE*

(A) (Contract) West Barnes Asthma Center, St. Louis, MO

(B)

6. INCLUSIVE DATES AND TOTAL COSTS OF THIS SPECIFIC PROJECT RELATED TO EACH 12 MONTH PERIOD IF MORE THAN ONE YEAR IS REQUIRED TO COMPLETE PROJECT. SUMMARIZE FROM BUDGET PAGE, ITEM 12(J). IT MUST BE UNDERSTOOD THAT AWARDS FOR 2ND AND 3RD PERIODS ARE DEPENDENT ON CENTER APPROVAL OF CONTINUATION APPLICATION.

	INCLUSIVE DATE			TOTAL COST
(A) 1ST 12 MONTH PERIOD	January 1, 1994	THRU	Dec. 1994	$ 196,875
(B) 2ND 12 MONTH PERIOD IF REQUIRED	1/1/95	THRU	12/31/95	$ 188,750
(C) 3RD 12 MONTH PERIOD IF REQUIRED	1/1/96	THRU	12/31/96	$ 188,750

7. INSTITUTIONAL OFFICER NAME, TITLE AND TELEPHONE NUMBER OF INDIVIDUAL AUTHORIZED TO SIGN FOR THE INSTITUTION IDENTIFIED IN #4 ABOVE. IT IS UNDERSTOOD THAT THE OFFICER, IN APPLYING FOR A CONTRACT, HAS READ AND FOUND ACCEPTABLE THE CENTER'S MANAGEMENT OF RESEARCH CONTRACTS AND CONTRACT ADMINISTRATION POLICY.

(A) Allen W. Mathies, Jr., M.D. (B) President & Chief Executive Officer
NAME TITLE
(C) 818-397-5555 (D) Allen W Mathies Jr (E) 5/27/93
TELEPHONE SIGNATURE OF INSTITUTIONAL OFFICER DATE

8. PRELIMINARY STUDIES*.
(A) FEASIBILITY OF PROPOSED RESEARCH
(B) QUALIFICATIONS OF INVESTIGATOR

9. EXPERIMENTAL PLAN*.
(A) DESIGN
(B) METHODS
(C) ANALYSIS OF DATA
(D) INTERPRETATION OF RESULTS
(E) TIMETABLE FOR THE INVESTIGATION
(F) LITERATURE CITED

10. AVAILABLE FACILITIES AND RESOURCES.

11. OTHER SUPPORT

*APPEND AS MUCH MATERIAL AS REQUIRED. TYPE, SINGLE SPACE, USE 8-1/2" X 11" WHITE PAPER AND LABEL EACH SHEET WITH NAME OF THE PRINCIPAL INVESTIGATOR IN THE UPPER RIGHT HAND CORNER AND PAGE NUMBER AT THE BOTTOM. CONSECUTIVELY NUMBER EACH ADDENDUM BEGINNING WITH PAGE 5. DO NOT INSERT PAGES BETWEEN PAGES 1 AND 6, E.G., 2A, 2B, 3A, ETC. INCLUDE NINE COPIES AND AN ORIGINAL. IF BINDING PHOTOGRAPHS, INCLUDE 2 ORIGINAL SETS. NOTE: EACH OF THE NINE COPIES *MUST* BE PLACED IN A BINDER PER MAILING INSTRUCTIONS.

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R: REDACTED MATERIAL

12.BUDGET. Detailed specific needs for the first 12-month period. Estimate category sub-totals for 2nd and 3rd periods, if required. Append justifications.

(a) Salaries, List personnel by name and title. Indicate individuals % time to be spent on this project.	$ 1st period	$ 2nd period	$ 3rd period
% Professional: M. Michael Glovsky,MD,P.I.20% Chin Chen Chou, Ph.D. MPH 100% M. Park, R.N. 50%			
% Technical: Vivian Mishalany 25%			
% Other:			
Fringe benefits payable at institution's rate of 25 %			
Category (a) Sub-Total			
(b) Consultants (per diem, travel & expenses): 1 Trip to St. Louis and 1 Trip to L.A. per year			
Category (b) Sub-Total			
(c) Supplies & Expense: Consumables (by category) Nitrogen Tanks Chemicals, glassware Stamps, mailings (x500) x 3/yr Lab Tests ..$.30.x.200..... ~~Animals and related costs~~ Service Contract (GC/MASS SPEC)			
Other expenses (itemize)			
Category (c) Sub-Total			
(d) Travel Expenses:			
Category (d) Sub-Total			
(e) Alterations and Renovations			
Category (e) Sub-Total			
(f) Sub-contracts Dr. Phillip Korenblatt St. Louis Studies			
Category (f) Sub-Total			
(g) Equipment Ozone generator			
Category (g) Sub-Total			
(h) TOTAL DIRECT COSTS	1		
(i) Indirect costs not to exceed 25% of the sum of (a) thru (f):			
(j) TOTAL PROJECT COSTS			

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13. BIOGRAPHICAL SKETCH of all professional personnel listed in 12(a). Append. Please include the following: Name, title, education, scientific field, major research interest, research and/or professional experience and publications. (Limit list of publications to the 20 most important and/or relevant.)

14. a) Are HUMAN SUBJECTS to be used in this research? X Yes _____ No
If yes, attach Institutional Review Board approval for procedures involving human subjects.

b) Are LABORATORY ANIMALS to be used in this research? _____ Yes X No
If yes, attach Institutional Animal Care and Use Committee approval for procedures involving animals.

15. SIGNATURE OF PRINCIPAL INVESTIGATOR: It is understood that the applicant in applying for a Contract has read and found acceptable the Statements of Policy and Terms Under Which Project Contracts Are Made appearing in the application package.

M. Paul Glimcher 5/27/93

Signature of Principal Investigator Date

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8. PRELIMINARY STUDIES

A. Feasibility of the Proposed Research

The effect of ozone, dog and cat allergens, and environmental tobacco smoke on lung function in Seniors exposed to high levels of air pollution (20-80 years) has not been studied. A fitting scenario is the San Gabriel Valley, one of the areas of highest air pollution in the United States for the past forty years. The setting of a basin, surrounded by mountains and the ocean, with high temperatures and relatively stagnant air flow, leads to high levels of oxidants from automobile omissions and photochemical oxidation products. In addition, burning of fossil fuels from industry adds sulfur dioxide and particulates to the air. High levels of pollen and microorganisms from year-round vegetation also account for respiratory difficulties among the one million residents in the San Gabriel Valley. By comparing the relative effects of ozone (a major irritant in smog); animal dander sensitivity; and ETS in the indoor environment, we will assess the relative contributions of each of these factors in altering lung function.

To our knowledge, no studies in seniors who have been exposed during the peaks of air pollution in the Los Angeles Basin have focused on progression of lung disease factors such as reactions to dogs and cats, ozone, and ETS.

The relative prevalence of asthma or hyperreactive airways disease in the elderly in the San Gabriel Valley is unknown. A study of seniors in Great Britain in a small rural community showed that 60% of aged individuals had abnormal pulmonary function, and that two-thirds of these patients had asthma.[1] Of interest was the fact that 90% were undiagnosed prior to the study and that the use of bronchodilators reversed the abnormal lung function.[2] Thus, it appears that asthma may be relatively under-diagnosed in the elderly. Additional components of extrinsic allergy in the development of asthma in the elderly also are unknowns in a high smog setting as well as a setting involving exposure to pets and ETS.

PATIENT POPULATION AND EXPOSURE CHAMBER

The sample to be used in all of the research listed below will come from the Senior Care Network, a diverse multi-racial group aged 50 to 90 years, who reside in the San Gabriel Valley -- one of the worst smog areas in the State of California. The Valley stretches from Pasadena to Pomona, with a population of approximately 1,000,000. The 15,000 member Network is sponsored by the Hunting-

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ton Memorial Hospital, a 101-year-old teaching institution located in Pasadena.

The new stainless steel Challenge Chamber, recently installed in HMH's Asthma and Allergy Center under the direction of Dr. M. Michael Glovsky, principal investigator, and Dr. Chin Cheng Chou, will be used for smoke and smog component exposure research. Jet Propulsion Laboratories, California Institute of Technology, advisors assisted in the design of this $100,000 Challenge Chamber.

STUDY OF THE EFFECT OF OZONE, A POLLUTANT, DOG AND CAT ALLERGENS, AND ENVIRONMENTAL TOBACCO SMOKE (ETS) ON ASTHMA AND LUNG FUNCTION

Ozone, the main irritant in smog, will be blown into the Challenge Chamber. Lung function and airways hyperreactivity will be determined in Seniors with normal and abnormal lung function. The effect of ETS on lung function will be determined in the presence and absence of ozone. Thus, new data will be obtained in Seniors exposed to ozone and ETS.

THE EFFECT OF CAT AND DOG DANDER ALLERGENS ON LUNG FUNCTION

Seniors with normal and abnormal lung function will be tested for allergic responses to dog and cat dander inhalation. The relative role of allergic airways disease and presence or absence of pets in the household will be determined. By removing pets from the household, the effect on lung function will be assessed. Dog and cat allergen will be measured in household dust to study exposure and asthma relationships.

ASTHMA AND SMOKING

In a large epidemiologic study of adults, the presence of asthma was not associated with a prior history of smoking.[3] Yet in some studies, bronchial hyper-responsiveness was found to be associated with current smokers and not past smokers.[4,5] Rijcken in a larger group studied than above found no association between current smokers and asthma.[6] Thus, the role of ETS in the causation of asthma is unclear. It is likely that other factors such as atopy, smog (ozone), presence of dogs and cats in the household, and location of residence, high versus low smog area could influence the development of asthma. We plan to study the relative role of ETS, cat and dog dander exposure, and ozone inhalation in the indoor air to assess the relative roles of each factor in the development of asthma in Seniors.

In summary, we believe our proposed research addresses several of the Center for Indoor Air Research Program Priority Areas, namely:

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asthma, a pulmonary disease; environmental tobacco smoke and relationship to smog; and presence or absence of pets, dogs and cats in the household. The sample used will provide ethnic and racial diversity. Important new data related to lung disease will result from our proposed research.

8. B. Qualifications of Investigator and Background of Studies

CONTRIBUTIONS TO ASTHMA STUDIES

For the last 20 years, I have been interested in the mechanisms of bronchial asthma. Starting in 1975, we did initial studies on the effect of air pollution on asthma in the Kaiser Permanente Medical Group patient population. We found that air pollution in 1976 was not associated with an increase in clinical severity of asthma.[7] At that time, the relative levels of ozone, nitrogen dioxide and sulfur dioxide were below the amounts that were required to induce clinical asthma. A surprising finding was that patients with dogs and cats had significantly worse asthma than allergic patients without pets. Other studies have looked at the effect of smog on children in the second and fifth grades and have found that those residing in high levels of smog areas were more likely to have asthma by spirometry and clinical history than those who were in lower smog areas. To our knowledge, no one has studied the effect of smog on seniors exposed to high levels of smog. Of note is the fact that the smog levels were higher from 1962 to 1972 than those from 1972 to 1992. For this reason, studies of seniors would be more relevant as far as long-term effects on lung function.

8. C. Background for Studies

Earlier studies have indicated that challenge with ozone at levels 0.14-0.18 parts per million, with exercise, was associated with a drop in expiratory lung volumes. Yet studies to determine whether clinical asthma was worse in times of high levels of O_3, NO_2 and SO_2 in our clinic demonstrated no change in clinical symptoms of asthma during high smog periods.[7]

Higgins, et. al. were not able to demonstrate significant drops in lung function in adolescents exposed to high levels of ozone.[9] Pierson, et al. had shown that exercise in high levels of ozone was associated with a drop in lung function under experimental chamber controlled studies.[8]

To our knowledge, no studies in seniors who have been exposed during the peaks of air pollution in the Los Angeles Basin have focused on progression of lung disease as a function of factors such as exposure to dogs and cats, ozone, and ETS.

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Previous studies on the relationship of smog to clinical asthma have been equivocal as to whether ambient air levels of ozone, nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) are relevant in the causation of asthma in the San Gabriel Valley.[10] To study this question, over the last two years we have solicited aid through a newsletter to individuals in the Senior Care Network. After an initial ad, 80 seniors responded and attended an education session. Thirty of those in attendance filled in a questionnaire and performed initial spirometries. Among this group there were 13 asthmatics. Ten out of 30 were former smokers. Only 4 of 10 former smokers had abnormal lung function. The combination of exposure to ETS and residence in an area of high air pollution seemed to be associated with more severe asthma. A control group of asthmatics from St. Louis (where air pollution is less) showed similar lung function between asthmatics who were smokers and non-smokers. Thus, we would like to study the effect of smog (ozone), ETS, and pet exposure in indoor air to sort out contributory factors leading to lung disease in seniors.

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9. RESEARCH PLAN

A. Specific Aims

1. Identify the prevalence of asthma in the elderly population in the San Gabriel Valley. Determine the length of residency among enrollees in the San Gabriel Valley and correlate their lung function with the pollution records over the last 30 years.

2. Determine the percentage of loss of pulmonary function and the reversibility factor in the population through baseline tests. Determine the prevalence of smoking or past smoking on seniors in the San Gabriel Valley.

3. Determine the relative incidence (new cases) of asthma in the Senior Care Network over a three-year period.

4. Study the effect on asthmatics of ETS in a challenge chamber. Both direct and second-hand smoke will be studied. Analyze the effect of smoking filtered cigarettes in the challenge chamber on lung function.

5. Study the effect of ozone exposure on smokers and non-smoking seniors. The effect of ozone plus smoking in the chamber will also be analyzed. Measure indoor O_3 concentration in high and low pollution days.

6. Analyze the number of seniors with dogs and/or cats at home and compare allergic status through skin testing and challenge studied with lung function. Measure concentrations of dog and cat allergens in house dust.

7. Follow a group of 50 senior asthmatics in St. Louis as a control site with relatively low levels of air pollution. Correlate ozone, NO_2 levels, SO_2 levels and smoking history with asthma.

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9. B. Methods of Procedures

1. 1,000 members of the Senior Care Network will be prospectively evaluated. They will be asked to fill out an asthma questionnaire. Five hundred will be recruited to perform lung function tests to determine whether they have bronchial asthma or abnormal lung function. The amount of time that they have lived in the San Gabriel Valley will be documented. Also, the city in which they live and the relative exposure to smog will also be documented. Presence or absence of cats and dogs will be recorded.

2. Of the original 1,000 individuals screened, it is estimated that 10-20%, or 100 to 200, will have abnormal lung function. This group will then be followed for the remainder of the grant period. Their medical history will be carefully evaluated. Lung function will be periodically monitored by spirometry, and the patients would themselves monitor on a weekly basis their peak flow rates.

3. New cases of asthma will be determined by questionnaire every six months and peak flow measurements. Patients having new symptoms of asthma will be invited to the clinic to perform spirometry and for a brief history and physical to determine if asthma has occurred.

4. Cat and dog dander allergies: Attempts to control exposure to cats and dogs will be performed. Those patients successfully removing cats and dogs from the household will be compared to patients with continued pet exposure.

5A. Challenge chamber testing will be performed with smoking asthmatic and non-asthmatic patients. Six groups of 10 patients will be studied with 10 and 20 standard cigarettes smoked in a four-hour period. One smoker and a companion non-smoker will be studied per day. Methacholine sensitivity will be assessed one day before smoking challenge and one day after smoking challenge. Lung function will be assessed 1, 2, 4, 8, 12, 20, 24 hours after smoking challenge.

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Six groups will be studied (see Table 1):

1) Smoking asthmatics;
2) Non-smoking asthmatics;
3) Smokers with lung function abnormalities but without asthma;
4) Non-smokers with lung function abnormalities, but without asthma;
5) Smoking patients with normal baseline lung function;
6) Non-smoking patients with normal lung function. The non-smokers will be studied for second-hand smoke effects on the lung.

Table 1
Evaluation of Smoking With or Without Ozone on Lung Function

Types of Patients	Test Parameters			
A. Asthmatics	Clean Air	*Ozone	Standard Cigarettes	Filtered Cigarettes
1. Smokers				
2. Non-Smokers				
B. Non-Asthmatics				
3. Smokers--abnormal (fixed) lung disease				
4. Non-Smokers--abnormal (fixed) lung disease				
5. Smokers--normal lung function				
6. Non-Smokers--normal lung function				

*Ozone will be tested alone and with standard cigarettes.

5B. The patients will be studied with smoking plus ozone (0.200 PPM) injected into the chamber to assess smoking plus or minus ozone. A third set of experiments with the same patients will study the effect of ozone alone in a four-hour exposure.

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6. Standardized filtered cigarettes will be used to study the effects (lung function) in an additional group of 10 smokers and non-smokers.

7. Chamber monitoring. Ozone and carbon monoxide will be monitored with a Miran 1A monitor. Air samples will be drawn from the chamber during smoking and measurements of acrolein, formaldehyde, particulates, and other irritants determined by gas chromatography, mass spectroscopy and chemical analysis. The chamber will be standardized for smoke-induced emissions in the first year. Smoking and non-smoking asthmatics will be studied in the second and third years.

The Huntington Memorial Hospital challenge chamber is outlined in an abstract (Appendix 1) and Figure 1. It is 4 feet 2 inches wide x 6 feet 2 inches high by 7 feet 2 inches long. It can easily accommodate two individuals comfortably. The chamber is lined with stainless steel and provides a clean filtered air source. Air entering the chamber is filtered through charcoal and HEPA filters. Gases or vapors are aerosolized with N_2 and blended into the chamber. Lamina flow is provided by a honeycomb (stainless steel) screen and a distal exhaust system. Slightly negative pressure is maintained in the chamber to prevent leakage. Target concentrations of gases are maintained within 10% projected levels. The test subjects enter the chamber through an air lock that minimizes changes in concentration. Access ports are provided to monitor chemical or physiologic measurements, pulse, blood pressure, or oxygen saturation. The advantage of this chamber is to quantify and monitor precise concentrations of chemicals, such as ozone, and to permit steady state parameters.

Ozone will be generated by an ozone apparatus (PC1 Ozone Corporation, West Caldwell, NJ) at a constant concentration of 0.2 PPM. Smoking challenge will be done with smokers smoking 10 to 20 standard cigarettes (2R1 - Reference cigarettes from the Tobacco Research Institute, University of Kentucky). 1R4F Filtered standard cigarettes will be compared with non-filtered cigarettes for their effect on lung function.

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Monitoring ETS in the chamber. The level of tobacco smoke will be monitored by measuring CO, acrolein, formaldehyde and nicotine and particulate concentration in the air by the methods of Stankus and Menton.[11,12] The level of tobacco smoke exposure will be measured by the concentrations of nicotine in the urine and saliva at 4 hours, 8 hours, 24 and 30 hours after challenge by G.C./Mass. Spec. A Hewlett Packard 5890-A Gas Chromatograph/5790 B Mass Selective Detector will be used. Tobacco smoke will be extracted from XAD-2 Tenax GC charcoal tubes and analyzed by a G.C./Mass. Spec. method as described.[13] The smoke will be generated through a smoking machine, available at Tulane Medical School. Relative concentrations of smoke components will be compared in filtered and non-filtered cigarettes.

8. Assessment of cat and dog allergic disease: Skin tests will be performed using standardized cat and dog dander extracts (ALK-USA). Relative airways reactivity will be measured by bronchial challenge testing. Ten cat and ten dog dander sensitive patients will be studied by quantitative nebulization of 1/100,000, 1/10,000 and 1/1,000 W/V extracts using a compressor nebulizer as described. Also, non-allergic patients, five dog owners and five cat owners with normal lung functions, will receive challenge tests as controls. Spirometries will be performed after each allergen dilution to determine PD_{20} endpoints of sensitivity. After removal of pets from the home (one and two years later) repeat challenge tests and lung function will be tested to determine the efficacy of cat and dog removal (re lung function). Controls will also be retested.

9. Indoor Air Sampling for Ozone, and Dog or Cat Allergens:

Indoor Air Ozone Sampling: The relative amount of ozone in indoor air has received little attention compared to outdoor air pollution measurements. Using a volumetric air sampling device (midget impinger) for ozone, we shall measure the relative amount of indoor ozone in 20 households from Pasadena and 20 households in St. Louis during both high, October, and low air pollution times. Care

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will be taken to measure homes with central air conditioning and filtration systems and other homes lacking air conditioning where open windows provide ventilation. Clinical symptoms of asthma will be assessed during the air sampling times. In addition, pollen counts will be determined weekly to provide data on outside aeroallergen exposure. It is possible that "priming" (allergen triggering) during the pollen period could make exposure to ozone, ETS, and cat and dog allergens worse.

Cat and Dog Allergens: Dust sampling using an Anderson impinger[14] will be used to measure Cat allergen (Fel dI) and Dog allergen (Can fI) in the collected dust samples. Radioimmunoassays will be used to measure the presence and absence of FEL dI and Can fI in the homes with and after removal of dogs and cats respectively.[15,16] Relative concentration of allergens will be measured both in the living room and bedrooms of patients.

9. C. Analysis of Data

Data will be analyzed and tabulated using statistical methods such as the following:

1. Student's T test for matched samples with normal distribution.

2. Regression analyses: to measure dose response relationships such as amount of cat allergen Fel dI versus FEV_1, in allergic patients.

3. Multiple determinations of lung function tests, in vitro IgE specific assays will be performed and means +/- standard deviations and coefficient of variation will be calculated.

Challenge testing with allergens will be quantified to determine PD_{20} values -- dose of dog or cat allergen that produces a 20% fall in FEV_1 (amount of air expired in one second after a complete inhalation).

Indoor air concentrations of ozone, dog and cat allergens will be determined and compared with specific challenge test requirements to alter lung function.

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Relative lung function will be compared in individuals with allergic asthma, non-allergic asthma, normals, and patients with restrictive lung disease after exposure to ETS, ozone, and dog and cat allergens.

9. D. Interpretation of Results

Results will be interpreted by statistical evaluation of objective measurements. Quantitative data will be obtained whenever possible.

Lehrer et al.[17] demonstrated, in a static smoke exposure environment that both asthmatics and non-asthmatics developed bronchial hyperreactivity after exposure to ETS. The drop in lung function and development of bronchial hyperreactivity could be significantly blocked by prior treatment with chromolyn and albuterol.[18] Among our seniors, the relative response to ETS is unknown. After initial studies, the effect of pretreatment with anti-inflammatory agents, chromolyn and potent topical inhaled steroids, aerobid or fluticosone will be tested. Our chamber is a dynamic chamber, with one change in air/minute of exposure and will provide interesting data compared to the static chamber as studied by Salvaggio and Lehrer.

Of interest as well is a comparison of exposure in the household to dog and cat allergens. Such quantitative exposure (ng/ml Fel dI and Can fI) focused on the household dust will be compared to inhaled concentrations of allergens required to produce a 20% fall in FEV_1 (PD_{20}). Such quantitative data may amplify that reported by Platts-Mills et al[19] and may be useful as a guide to reduce animal dander exposure in the home and workplace. No studies of dog dander control have yet been performed.

9. E. Timetable of Investigation

1st Year:

1. Submit recruiting letter to 1,000 randomly selected Seniors. Follow up with phone calls to be sure that 1,000 people recruited are willing to participate in study.

2. Perform spirometrics and total IgE in 500 Seniors who have symptoms of lung disease, asthma, or allergic nasal disease, as determined by questionnaire.

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3. Standardize challenge chamber and measure cigarette smoke metabolites and air samples with normal volunteers in the chamber in the presence and absence of ETS. Measure spirometrics of normals and test for hyperreactivity.

4. Perform repeat spirometries on patients with newly acquired asthma at 6 and 12 months to determine new asthma cases.

5. Measure dust and air samples in homes of asthmatics with and without cats and dogs. Determine reliability of ozone, FEL dI and Can fI assays in household air and dust samples. Do skin tests for allergy on 100 to 200 Seniors.

2nd Year:

1. Perform challenge tests in chamber with ozone and ETS in groups of six different patients, both smokers and non-smokers with normal and abnormal lung function (total 60 patients).

2. Perform bronchial challenge tests in allergic and non-allergic patients who have and those who do not have dogs and cats at home.

3. Follow lung function of 100 to 200 patients with questionnaires and Peak Flow Rate determinations in asthmatics and normals every four months. Perform spirometries on new cases of asthma determined by questionnaire.

4. Remove cats and dogs from the house in individuals with allergic asthma and repeat bronchial challenge tests at six-month intervals. In those allergic asthmatics to dogs and cats who continue to have pets at home repeat challenge tests.

5. Measure indoor air and dust for ozone and dog and cat allergens on a twice yearly basis in selected households.

3rd Year:

1. Continue to measure spirometries in 100 to 200 patients with normal and abnormal lung function (three times per year).

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2. Seek out new asthma cases in 1,000 Seniors through questionnaire. Perform spirometries in suspected new cases.

3. Perform repeat bronchial challenge tests on patients with and without dogs and cats.

4. Measure air and dust samples in selected households.

5. Challenge new group of patients to ETS and ozone in chamber.

6. Analyze metabolites from ETS, challenge volunteers with formaldehyde, nicotine, at NIOSH acceptable amounts.

7. Analyze data for publication.

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Source: https://www.industrydocuments.ucsf.edu/docs/gjnm0000

References

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2. Banerjee, D.K., Lee, G.S., Malik, S.K., Daly, S. Underdiagnosis of Asthma in the Elderly. Br. J. Dis. Chest, 81, 23, 1987.

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4. Burney, P.G.J. et al. Descriptive epidemiology of bronchial reactivity in an adult population. Results from a community study. Thorax 42:38, 1987.

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BUDGET JUSTIFICATION

1. Dr. Chin Chen Chou: Dr. Chou has standardized our newly constructed Chamber. He has experience with gas chromatography, air sampling, and chemical analysis. He has extensive experience with Chamber monitoring and analysis of tobacco vapors, gases and chemicals.

2. Marty Park is an experienced pulmonary nurse and has done spirometries for several years.

   500 Spirometries will be performed in the first 6 - 8 months.
   1,000 questionnaires will be mailed to randomly selected seniors.

3. Dr. Phillip Korenblatt, Head, West Barnes Hospital, St. Louis, MO., Clinical Professor of Medicine, Washington University. Directs a large Asthma Center with full lung function and rehabilitation programs. The St. Louis patients will serve as low pollution controls.

   Dr. Korenblatt perform skin tests on asthmatics and measure ozone and and dust samples in selected homes. He also will perform spirometires on 50 patients twice per year.

4. Mailing costs are 29c x 1,000 questionnaires sent four times in the first year. Stamped, return envelopes are included 2 x 1 year, for a total cost of $1,740.00. These expenses will occur also in the second and third year.

5. $2,000 is required to help pay for UCLA - G.C./Mass Spec maintenance contract, as well as, columns and supplies.

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KEY PERSONNEL

Name, Degree(s)	Position Title, Department, and Institution	Project Role
1. M. Michael Glovsky, M.D.	Medical Director, Huntington Memorial Hospital Asthma Center	Principal Investigator
2. Chin-Cheng Chou MS, DVM, Ph.D. Candidate	Industrial Hygienist Asthma Center, Research Associate, Teaching Assistant, UCLA School of Public Health	Supervise Challenge studies, monitor chemicals and gases in chamber
3. Marty Park, R.N.	Nurse Practitioner	Organize patient appointments, measure lung functic Assess questionnaires and peak flow charts.
4. Vivian Mishalany, B.A.	Asthma Center	Type correspondence and forms, mailings
5. Phillip Korenblatt, M.D.	Director, West Barnes Hospital Asthma and Allergy Center	Supervise Asthma patients, St. Louis

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Principal Investigator: M. Michael Glovsky, M.D.

BIOGRAPHICAL SKETCH

M. Michael Glovsky, M.D.

NAME

ROLE IN PROJECT

EDUCATION. Begin with baccalaureate and end with most recent, including postdoctoral training.

Institution and Location	Field of Study	Degree	Year
Tufts University, Medford, Mass.	Chemistry-Biology	B.S.	1957
Tufts Medical School, Boston, Mass.	Medicine	M.D.	1962
Baltimore City Hosp, Baltimore, MD	Intern		1962-63
New England Med. Center, Boston, MA	Medical Resident		1965-66
Special NIH Fellow, Allergy & Immunology	Fellow		1966-69
Walter Reed Army Institute of Research, Washington, D.C.	Allergy and Immunology		1966-68
Univ. of California, SF	Hematology & Immunology		1968-69

RESEARCH AND PROFESSIONAL EXPERIENCE. *In chronological order, list:* (1) All professional positions, including title, institution, and years of appointment. (2) Complete citations of all publications in the last 5 years or less, and earlier pertinent publications. List all authors in order. If investigator published under another name, underline that name. **DO NOT EXCEED TWO PAGES.**

Huntington Memorial Hospital, Pasadena, California, Director, Specialized Lung Asthma, Allergy, and Immunology Center, 1989 -

Clinical Professor of Medicine, USC, 1989-

Clinical Professor of Pathology, USC, 1989-

Professor of Medicine, USC, School of Medicine, 1984-1989

Clinical Professor of Medicine, University of California, Los Angeles, 1983-1984

Visiting Associate in Chemistry, California Institute of Technology, Pasadena, 1977-present

Professor of Pathology, University of Southern California, School of Medicine, 1986-1989

USC, School of Medicine, Department of Medicine

*Director L.A. Co. General Hospital/USC Asthma Clinic, 1984-1989

*Head, Allergy & Immunology Labs, Pulmonary Division, 1984-1989

Southern California Permanente Medical Group, 4900 Sunset Blvd., Los Angeles, CA, 1969-1984

*Co-Director, Residency Program in Allergy & Clinical Immunology Kaiser Hospital, Los Angeles, 1974-1984

*Staff Physician, Department of Internal Medicine, 1969-1972

*Director, Allergy & Immunology Laboratory, 1970-1984

*Chief, Department of Allergy & Clinical Immunology, 1974-1984

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Dr. M. Michael Glovsky

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55. Glovsky MM, Farrow N, Ross B, Ward PA, Morganroth M: Hypoxic and complement induced lung injury in the isolated perfused rat lung as determined by 31 phosphorous nuclear magnetic resonance. In press - Int Arch Allergy Appl Immunol, 1992.

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CHOU, CHIN - CHENG, M.S., D.V.M.

EDUCATION:

National Taiwan University Taipei, Taiwan	Veterinary Medicine	B.V.M.	1985
Dep. of Examination, R.O.C. Taipei, Taiwan	Veterinary Medicine	D.V.M.	1986
Chinese Taipei Modern Pentathlon and Biathlon Associ. Taiwan	Intern		1986-1987
Tulane University New Orleans	Public Health	M.S.	1989
University of California., Los Angeles	Environmental Health	Ph.D. Candidate	1992

EXPERIENCE:

Consultant Huntington Memorial Hospital, Asthma and Allergy Center 1991-

Teaching Assistant UCLA Department of Environmental Health Sciences 1992-

Staff Research Associate UCLA Department of Environmental Health Sciences 1990-

Graduate Student Researcher UCLA Department of Environmental Health Sciences 1990-1991

Research Assistant Tulane University Pulmonary Disease Section 1989

Doctor of Veterinary Medicine Chinese Taipei Modern Pentathlon and Biathlon Asso. 1986-1987

Editor-in-chief Journal of Veterinary Medicine, NTU. 1982-1983.

ARTICLES:

SEPARATION OF pH, IONIC STRENGTH, AND CHEMICAL MATRIX EFFECTS FOR BIOLOGICAL MONITORING OF URINES WITH THE MICROTOX TEST USING NICOTINE, COTININE, AND REFERENCE URINES. Chin C. Chou and Shane S. Que Hee
Journal of Bioluminescence and Chemiluminescence, In press.

CHARACTERIZATION OF THE O-(2,3,4,5,6 PENTAFLUROBENZYL)HYDROXYLAMINE HYDROCHLORIDE (PFBOA) DERIVATION OF SOME ALIPHATIC MONO- AND DI-ALDEHYDES AND RUGGEDIZATION OF WATER ANALYSIS OF THESE ALDEHYDES. Devon A. Cancilla, Chin-Cheng Chou and Shane S. Que Hee. Journal Of AOAC International 75, 842- 854 (1992).

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MICROTOX EC_{50} VALUES FOR DRINKING WATER BYPRODUCTS PRODUCED BY OZONOLYSIS. Chou,C.C. and Que Hee, S.S. Ecotoxicology and Environmental Safety 23, 355-363 (1992).

THE PHOTOBACTERIUM BIOLUMINESCENCE BIOASSAY AS A BIOLOGICAL MONITORING METHOD. Chou, C.C. and Que Hee, S.S. paper presented at AIHCE, Boston, June 1992.

EVALUATION OF THE PERFORMANCE OF AN ASTHMA CHALLENGE CHAMBER. Chou, C.C. and Glovsky, M.M. paper presented at AIHCE, Boston, June 1992.

GC/MS OF A HOMOLOGOUS SERIES OF ALDEHYDE AFTER DERIVATIZATION. Cancilla, D.A., Chou, C.C., Que Hee, S.S. paper presented at AIHCE, Salt Lake City, May 1991.

PREDICTION OF THE EFFECT OF DUST LOADING ON FILTER PERFORMANCE. Kadrichu, N.P., Chou, C.C., Hinds, W.C. paper postered at AIHCE, Salt Lake City, May 1991.

MICROTOX TOXICITY AND OZONOLYSIS BY-PRODUCTS IN DRINKING WATER. Shane S. Que Hee, Devon A. Cancilla, C.C.Chou, Li-Jue Wu. paper postered at U.C.Toxic Substances Research and Teaching, Santa Barbara, November 1990.

TRAINING AND CARING OF EQUINE. China Times, September 1986.

DYSTOCIA OF GREEN ISLAND'S WHITE-SPOT DEERS. Agriculture Bullutin. N.T.U.,1985.

VETERINARY OCCUPATIONAL SURVEY. Journal of Veterinary Medicine, N.T.U., 1983.

FEEDING AND CARING OF LABORATORY ANIMALS. Journal of Veterinary Medicine II, N.T.U. 1983.

EPIDEMIOLOGICAL SURVEY OF GREEN ISLAND SPOT DEER DISEASES. Journal of Animal Medicine, R.O.C., 1984.

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Principal Investigator: Michael Glovsky, M.D.

BIOGRAPHICAL SKETCH

PHILLIP E. KORENBLAT, M.D. — NAME

ST. LOUIS-BASED CONSULTANT — ROLE IN PROJECT

EDUCATION. Begin with baccalaureate and end with most recent, including postdoctoral training.

Institution and Location	Field of Study	Degree	Year
Univ of Arkansas, Fayetteville AR	Biology	B.M.S.	1956
Univ of Arkansas School of Med Little Rock AR	Medicine	M.D.	1960
Jewish Hosp of St.Louis MO	Internal Med	Internship	1960-61
Jewish Hosp of St.Louis MO	Internal Med	Residency	1963-65
Scripps Cl & Research Foundation La Jolla CA	Allergy/Immun	Fellowship	1965-66

RESEARCH AND PROFESSIONAL EXPERIENCE. *In chronological order, list:* (1) All professional positions, including title, institution, and years of appointment. (2) Complete citations of all publications in the last 5 years or less, and earlier pertinent publications. List all authors in order. If investigator published under another name, underline that name. DO NOT EXCEED TWO PAGES.

POSITIONS:

Attending Physician/Allergy Consultant/ Co-Director of Allergy Clinic, Jewish Hospital of St. Louis, St. Louis MO 1966-Present

Attending Physician/Allergy Consultant, Barnes Hospital, St. Louis MO 1970-Present

Assoc Clinical Professor of Medicine, Washington University School of Medicine, St. Louis MO 1981-1988

Professor of Clinical Medicine, Washington University, St. Louis MO 1988-Present

Chief of Staff, Barnes West County Hospital, St. Louis MO 1989-1991

Director, The Asthma Center, Barnes West County Hospital, St. Louis, MO 1989-Present

SELECTED PUBLICATIONS:

"Allergy: Theory and Practice." Editors: Phillip E. Korenblat, M.D. and H. James Wedner, N.D. A textbook for the practicing physician. Publisher: Grune & Stratton, Inc. First Edition: 1984. Second Edition: 1992.

"Asthma Management." Phillip E. Korenblat, M.D. "Allergy: Theory and Practice." Grune & Stratton, Inc. Chapter 21, pp 309-324, First Edition 1984; Chapter 25, pp 397-410, Second Edition 1992.

"A Community-Based Asthma Center: The Washington University Model." Anne M. Pittman, M.D. and Phillip E. Korenblat, M.D. Insights in Allergy, Mosby-Year Book, Inc. Vol 6, No 2, June 1991.

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"Mastocytosis presenting as osteoporosis: A report of 10 cases." A. Chines, M.D., R. Pacific, M.D., S.L. Teitelbaum, M.D. P. E. Korenblat Presented to American Academy of Allergy & Immunology, October, 1989. Journal of Clinical Endocrinology and Metabolism, 72:140-144, 1991.

"Anticholinergic Agents in the Treatment of Asthma." H. J. Wedner, M.D. and P. E. Korenblat, M.D. A position paper on treatment of asthma. Prese to American Academy of Allergy & Immunology. Parameters for the Diagnosis and Treatment of Asthma, May 1989.

"Asthma Management: An Integrated Approach." Phillip E. Korenblat, M.D. Modern Medicine magazine, Vol 57/May, 1989.

"Chronic Cough." Anne Pittman, M.D., Daniel Schuller, M.D., Phillip Korenblat, M.D. Textbook: "Difficult Diagnosis II." W. B. Saunders. In press 1991.

"Anaphylaxis-Induced Myocardial Depression Treated with Amrinone." Elizabeth Otero, M.D., John R. Onufer, M.D., Craig K. Reiss, Phillip E. Korenblat, M.D., Lancet, Vol 337, No 8742, p 682, March 16, 1

"Management of Status Asthmaticus." Robert M. Senior, M.D., Stephen S. Lefrak, M.D., Phillip E. Korenblat, M.D. JAMA, Vol 231, No 12, pp 1277-1279, March 24, 1975.

Abstracts:

"Subclinical Mastocytosis Presenting as Osteoporosis." Korenblat, P.E., Avioli, L.V., Teitelbaum, S.L. New England & Regional Proceedings, Vol 9, No 4, pp 328 July/August 1988. Abstract presentation at the 13th International Congress of Allergology & Immunology, Montreux, Switzerland, October 21, 1988.

"Non-Decalcified Bone Biopsy in the Diagnosis of Mastocytosis." Phillip E. Korenblat, M.D. and S. L. Teitelbaum, M.D. Abstract presentation at National Meeting of American Academy of Allergy and Immunology, March 14, 1988.

"Four Slice Coronal CT as a Screen for Allergic Sinusitis." Wippold II, F.J., Levitt, R.G., Korenblat, P.E., Hodges III, F.J., Jost, R.G., Evens, R.G. Scientific paper presented at the 78th Scientific Assembly of Radiological Society of North American, November 29-December 4, 1992.

"Desipramine - Induced Eosinophilia, Bronchospasm and Pulmonary Infiltrates." T. King, M.D., J. R. Panuska, M.D., P. E. Korenblat, M.D. Presented at 12th International Congress of Allergology & Clinical Immunology. JACI, Vol 80, No 1, pp 18-23, 1987.

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Principal Investigator: Michael Glovsky, M.D.

OTHER SUPPORT

NONE

C3

Name _____ Active ___ Pending ___ None ___

Source/identifying no. _____

P.I. _____ Recipient Institution _____

Title _____

Current/requested annual direct costs _____ Project start and end dates _____

Specific aims of the project _____

Role, including title and brief description of responsibilities _____

Percent time commitment for any period(s) overlapping the proposed project award period: 1993-94 _____

1994-95 _____

1995-96 _____

Source of support for participation, if other than as a salaried employee of the recipient institution _____

Describe scientific and budgetary overlap _____

Describe adjustments to be made if the present application is funded (budget, % effort, aims, etc.) _____

Is the other research project relevant to tobacco-related disease as defined in this application? ☐ Yes ☐ No

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FACILITIES AND RESOURCES

FACILITIES: the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe the facilities at any other performance sites listed in Box 10, page 1, and at sites for field studies. Using continuation pages if necessary, include an explanation of any consortium/contractual arrangements with other organizations.

☒ Laboratory: Huntington Memorial Hospital Asthma Center and UCLA

☒ Clinical: 2500 square foot suite, 200 yards from the Huntington Memorial Hospital, and is a department of the hospital. The unit is staffed by 3 nurses; (one full-time and 2 part-time). Pulmonary function equipment includes 2 Multi Spiro spirometers. Allergy testing and bronchial and inhalation tests are routinely performed in the Center.

☐ Animal:

☒ Computer: Huntington Memorial Hospital Asthma Center and UCLA Computer system

☐ Office:

☐ Other (Laboratory space):

Laboratory space for radioimmuno assays is available at Huntington Memorial Hospital Research Institute, 660 South Fair Oaks Avenue, 1/2 block from the Asthma Center.

MAJOR EQUIPMENT: List the most import equipment items already available for this project, noting the location and pertinent capabilities of each. 1. Asthma Challenge Chamber, Huntington Memorial Hospital.
2. Ozone Generator, UCLA. 3. Gas chromotography/Mass spectrometry, UCLA.
4. Miran 1A analyzer, Huntington Asthma Center. 5. Smoking Machine, Tulane Medical Center.

Capability:
1. Challenge Study
2. Generate required Ozone concentration
3. Identification and quantification of chemicals
4. Measure and monitoring Ozone and Carbon Monoxide
5. Generate tobacco smoke
6. Perform rast tests for dog and cat allergens.

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such as consultants, secretaries, machine shop, and electronics shop, and the extent to which they will be available to the project.

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Principal Investigator: M. Michael Glovsky, M.D.

APPENDIX COVER SHEET

1. Abstract: Challenge Chamber
2. Figure 1: Outline of Challenge Chamber
3. Asthma Questionnaire
4. Consent Form
5. Reprint - Smog and Asthma

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VALUATION OF THE PERFORMANCE OF AN ASTHMA CHALLENGE CHAMBER

hou C.C., Department of Environmental Health Sciences, UCLA School of Public Health. 0833 Le Conte Ave., Los Angeles, CA 90024. Glovsky M.M., Asthma and Allergy Center, untington Memorial Hospital, 39 Congress Street, Suite 301, Pasadena, California 91105.

A large number of substances can cause allergic reactions. Some causes, such as molds, dust, or pollen, can be determined easily by skin scratch, intradermal, or blood tests. But some work related irritants and chemicals can cause occupational asthma. These chemicals must be determined in the field or diagnosed in a relative environment as determined by pulmonary function performance. Thus, an Asthma Challenge Chamber was constructed and evaluated to test for chemicals known to produce occupational asthma.

The chamber is lined with stainless steel and has an observation window. Entering room air is filtered to remove chemicals and dusts. It is operated at constant laminar flow and is also maintained at a slight negative pressure to prevent leakage. Vapors and gases of four chemicals, toluene diisocyanate (TDI), methylene bisphenylisocyanate (MDI), hexamethylene diisocyanate (HDI) and formaldehyde, were generated according to OSHA's Permissible Exposure Limit (PEL) and Time-Weighted Average (TWA) concentration by bubbler purge/trap or syringe pump flash evaporator generation systems. For TDI, MDI and HDI, target concentration were monitored by MDA-7100 Toxic Gas Monitor and compared with the Marcali spectrophotometric method. Formaldehyde concentration is detected by a Miran IA Gas Analyzer and calibrated by NIOSH analytical method number P&CAM125.

During the monitoring, chamber flow is controled at 180 cubic feet per minute and the target chemical concentrations are all within 7% confidence interval. Stability of concentration is obtained within 5 minutes after generation. Exhaustion of chemicals are reached 4 minutes after stopping generation. The patient's challenge reponse and psychological effects can be measured by pulmonary function testing and psychologic evaluation. In a work environment, multiple chemicals are found. With precise, steady state exposure, the Challenge Chamber can be a good evaluation and diagnostic tool to pinpoint specific chemicals that cause asthma in the workplace.

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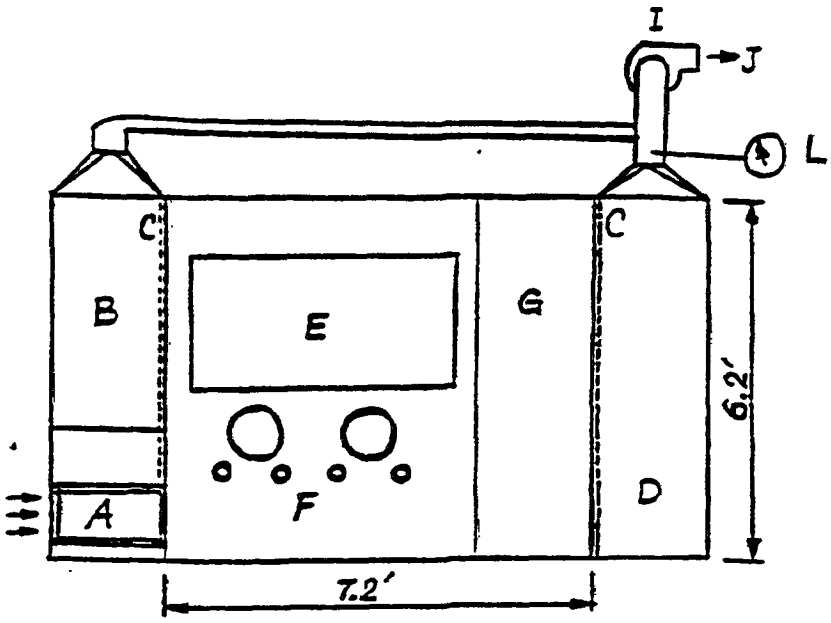
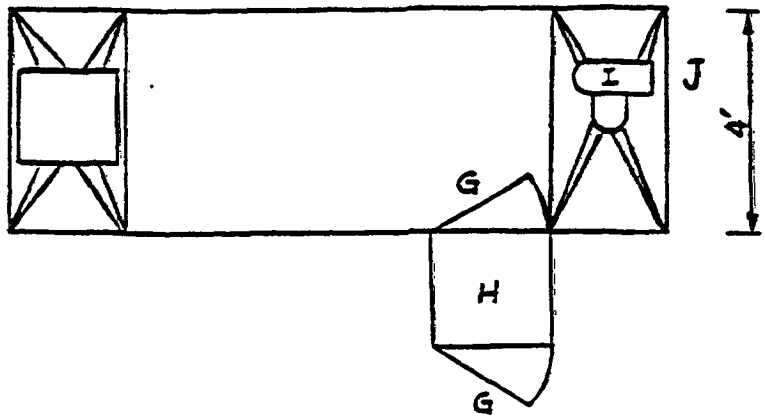
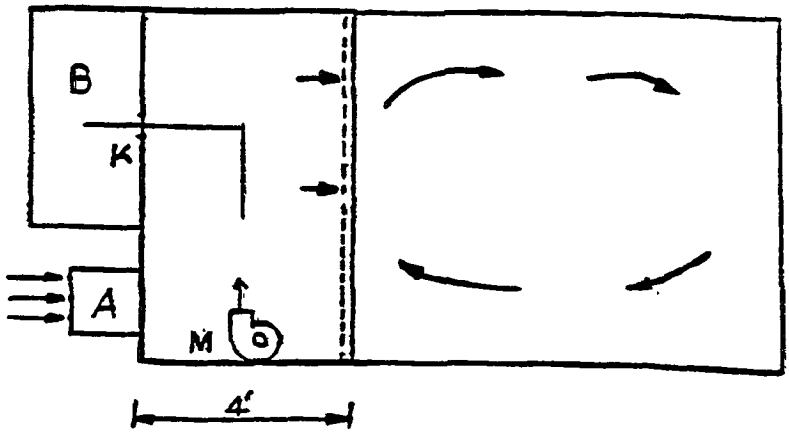




A. INTAKE FILTER
B. HOOD
C. DIFFUSION SCREEN
D. PLENUM
E. OBSERVATION WINDOW
F. PORTS
G. DOOR
H. AIRLOCK
I. BLOWER
J. EXHAUST
K. INJECTION PORT
L. PRESSURE GAUGE
M. MIXING FAN



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ASTHMA IN SENIORS
POSSIBLE RELATIONSHIP WITH SMOG

AME: _____

DDRESS: _____
Street

_____
City Zip Code

ELEPHONE NUMBER: ( )_____ SEX: _____

ODAY'S DATE: _____

IRTH DATE: _____

YMPTOMS RELATING TO YOUR CHEST OR BREATHING

1.	Have you had wheezing or whistling in your chest at any time in the last 12 months?	YES NO (circle)
	If "NO" skip to Question 2	
	If "YES"	
1.1	How old were you when you first had wheezing or whistling in your chest? (make the best estimate that you can)	_____ years old
1.2	Is your wheezing worse at any of the following times of the year?	
1.2.1.	February - June	YES NO
1.2.2.	July	YES NO
1.2.3	August - October	YES NO
1.2.4	November - January	YES NO
1.3	Is your wheezing better or worse on weekends?	(circle 1 no.)
	Better	1
	Worse	2
	Sometimes worse, sometimes better	3
	Neither worse nor better	4

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Tightness in the chest in the early morning

2. Do you sometimes wake with a feeling of tightness in your chest first thing in the morning? YES NO

If "NO" skip to Question 3
If "YES"

2.1 For how long does this tightness usually last? (circle 1 no.)

Less than 30 mintues	1
Less than 1 hour	2
More than 1 hour	3

2.2 Is this tightness usually relieved by medicines (including aerosols, inhalers, or pills?) YES NO

Shortness of Breath

3. Have you at any time in the last 12 months, had an attack of shortness of breath that came on during the day when you were not doing anything strenuous? YES NO

4. Have you, at any time in the last 12 months, been woken at night by an attack of shortness of breath? YES NO

Phlegm From the Chest

5. Do you usually bring up phlegm from your chest first thing in the morning? (Clearing your throat does not count). YES NO

If "NO" skip to Question 6

If "YES"

5.1 Have you brought up phlegm from your chest like this on most mornings for at least 3 months each year? YES NO

6. Which of the following statements best describes your breathing? (circle 1 no.)

I rarely if ever have trouble with my breathing	1
I do have regular trouble with my breathing, but it always gets completely better	2
My breathing is never quite right	3

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THINGS THAT MIGHT AFFECT YOUR CHEST OR BREATHING

Colds

7. When you have a cold or "flu" or other respiratory infection, do you usually:

7.1	Also get a cough?	YES	NO
7.2	Start to wheeze?	YES	NO
7.3	Get a feeling of tightness in your chest	YES	NO
7.4	Start to feel short of breath?	YES	NO

Smoking Rooms and a Smoky Atmosphere

8. When you are in a smoky room or smoky atmosphere do you usually:

8.1	Start to cough?	YES	NO
8.2	Start to wheeze?	YES	NO
8.3	Get a feeling of tightness in your chest?	YES	NO
8.4	Start to feel short of breath?	YES	NO

Animals, Dust, Feathers

9. When you are in a dusty part of the house or with animals (for instance dogs, cats, or horses) or near feathers (including pillows, quilts and elderdowns) do you ever:

9.1	Start to cough?	YES	NO
9.2	Start to wheeze?	YES	NO
9.3	Get a feeling of tightness in your chest?	YES	NO
9.4	Start to feel short of breath?	YES	NO
9.5	Get a runny or stuffy nose, or an attack of sneezing?	YES	NO
9.6	Get itchy or watering eyes?	YES	NO

Trees, Grass, Plants, Flowers or Pollen

10. When you are near to trees, grass or flowers, or when there is a lot of pollen about, do you ever:

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10.1	Start to cough?	YES	NO
10.2	Start to wheeze?	YES	NO
10.3	Get a feeling of tightness in your chest?	YES	NO
10.4	Start to feel short of breath?	YES	NO
10.5	Get a runny or stuffy nose, or attacks of sneezing?	YES	NO
10.6	Get itchy or watering eyes?	YES	NO

11. Does exercise or strenuous work ever make you:

11.1	Start to cough?	YES	NO
11.2	Start to wheeze?	YES	NO
11.3	Get a feeling of tightness in your chest?	YES	NO
11.4	Get suddenly short of breath?	YES	NO

ILLNESS THAT YOU HAVE HAD IN THE PAST, OR STILL HAVE

12.	Have you ever had asthma?	YES	NO
	If "NO" skip to Question 13		
	If "YES"		
12.1	Was this confirmed by a doctor?	YES	NO
12.2	How old were you when you had your first attack?	_____ years old	
12.3	Have you had an attack in the last 10 years?	YES	NO
12.4	Have you had an attack in the last 12 months?	YES	NO
12.5	Are you taking any medicines (including inhalers, aerosols or tablets) for asthma?	YES	NO
13.	Have you had attacks of "hay fever"?	YES	NO
14.	Did you have eczema as a child?	YES	NO
15.	Have you ever had pneumonia?	YES	NO
	If "NO" skip to Question 16		

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If "YES"

15.1 What year(s) did pneumonia occur? _____

_____

15.2 Were you hospitalized? YES NO

15.2.1 If yes, list years _____

_____

15.3 Was the pneumonia confirmed by X-ray? YES NO

15.3.1 If yes, list years _____

_____

16. Are you now or were you a smoker? YES NO

16.1 How many years have/did you smoke? _____ years

16.2 How many packs per day? _____ no. of packs

16.3 If you quit smoking, how many years ago? _____ no. of years

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Principal Investigator:
Michael M. Glovsky, M.D.

CONSENT FORM

STUDY: THE EFFECT OF ETS, DOG AND CAT ALLERGY, AND SMOG ON ASTHMA IN THE ELDERLY

Based on the findings of your asthma questionnaire and examination of the spirometries, you are invited to participate in this research study on the effect of ETS and smog on asthma. The purpose of this study is to examine the effect of smog, dogs and cats, and ETS on asthma. The study will attempt to discover whether there is a direct relationship between the three above factors. You will receive no medical benefit from participation in this study, although information provided from this study may possibly be of benefit to you as a potentially asthmatic patient and could be of benefit to other asthmatic patients who live in an area of high smog levels.

You and up to 60 other volunteers will be asked to do lung function tests. You will breathe into a computerized spirometer which will measure your lung function. This will tell us and you whether you have a reversibility in your lung capacity. If the lung capacity gets better and worse with time or with treatment, by definition you have bronchial asthma. We would like to follow your lung function by having you do periodic breathing into a peak flow meter over the next two and a half to three years.

In addition, we will solicit help of the asthmatics in the study and some normals. We will attempt to identify whether ETS, dogs and cats, and the component of smog, ozone, are related to worsening asthma. To do this, we will ask you to spend from two to four hours in a "challenge chamber." While in this chamber, one of you, a smoker, will smoke ten or 20 cigarettes over a two or four hour period. During this time, periodically your lung function will be analyzed with a comput-

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erized lung function analyzer. In addition, one of the two occupants of the chamber will be a non-smoker. The non-smoker will serve to help define the effect of second-hand smoke on the airways function.

In addition, a second group of experiments will include smoking plus ozone in individuals exposed to both in the challenge chamber. The amount of ozone introduced into the chamber will be essentially the same as that in a first stage smog alert or 0.200 parts per million of ozone within the chamber.

This is a relatively small amount of ozone and, by itself in non-exercising individuals, should not induce asthma.

At the beginning of the study, you will perform lung function tests to determine whether or not you have asthma.

A very preliminary physical exam and history will be taken at the beginning of the study.

Your lung function, as mentioned above, will be monitored over a period of two and a half to three years. A number of individuals, 60 or more, will be asked to participate in the challenge chamber studies. These studies will involve anywhere from two to four hour sessions within the chamber. Prior to going into the chamber to be tested for smoke or ozone sensitivity, your lung function will be measured, and a measurement of lung hyperreactivity will be performed. To test for lung twitchiness, you will be asked to inhale relatively small amounts of a chemical called methacholine. This chemical causes bronchial constriction. Your lung function will be measured after varying amounts of the chemical to see if, by definition, you have asthma. If your lung function gets worse when inhaling this chemical, you will be given two puffs of Albuterol to reverse the asthma and make your lung function better.

During the chamber studies, it would be useful to get sputum and saliva and urine samples to measure the effect of cigarette smoke on fluids in your body. In addition, other chemicals within the chamber will be carefully monitored so that there is little or no danger from excess chemicals within the chamber.

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The study will last for a total of three years. You will be asked to keep a relatively simple diary to test whether your lung function and clinical symptoms are stable or whether there is some worsening in the asthma. In addition, we will measure the amounts of smog, ozone, nitrogen dioxide, and sulfur dioxide as well as particulates in an attempt to identify whether your lung function and those of others in the study are affected by different amounts of smog.

Dust and air samples will be collected from some patients' homes to measure ozone and dog and cat allergens. Some patients will be asked to get rid of dogs or cats to check the effect of pet removal on asthma.

Also, some dog and cat allergic patients will be tested for asthma by inhaling small quantities of dog or cat allergen solutions through a nebulizer. If asthma is provoked by animal extract inhalation, it will be reversed by Proventil inhalation.

Certain changes in body functioning can take place when any person is exposed to cigarette smoke. These can include but not be limited to coughing, wheezing, increased difficulty breathing, and feelings of nausea and malaise.

If during any time while you are in the challenge chamber you feel ill, we will encourage you to come out and to terminate the test immediately. While you are being tested in the chamber, you will be observed on a continuous basis, and if our investigators feel that it is of danger to you, we will ask you to immediately stop the testing.

You may choose to be treated or stop participation in the study at any time. Alternative therapies are available to you. While being tested in the chamber, it is necessary that you not take inhaled bronchodilators for 12 hours prior to the chamber testing. You may continue to take inhaled cortisone preparations and/or theophylline, which will not affect the results of our studies.

Should you desire to withdraw from the study, you may do so at any time for any reason without penalty or loss of benefits to which you are entitled. Participation is voluntary and

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refusal to participate will involve no penalty of loss of benefits to which you are otherwise entitled. All of the results of the study are available to your physician at any time, should he so desire to see them.

If, during the course and as a result of participation in the study, any physical injuries shall occur to you which is caused by any substance ingested or administered due to the protocol, you will be treated by the Asthma and Allergy Center immediately. There is little danger of severe or marked untoward reactions as a result of the challenge chamber testing.

If there is any other information that you would desire, I would be happy to provide it to you. By signing this form, you acknowledge that the scope of the testing has been described to you and that you willingly participate in this research study of the Huntington Memorial Hospital Asthma and Allergy Center.

Signatures

_____
Participant

_____
Witness

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As part of a multifactorial computer-assisted study of patients with asthma, the relationship between air pollution, animal dander and asthma symptoms was evaluated. No association was found between four major air pollutants (carbon monoxide, ozone, nitrogen oxides and sulfur dioxide) and asthma symptoms. Patients who owned cats and dogs reported more severe asthma symptoms ($p<.01$) than patients who did not own cats and dogs. The evaluations completed to date indicate that daily exposure to cats and dogs accounts for more of the asthma symptoms differences between patients than daily exposure to air pollutants.

A MULTIFACTORIAL STUDY OF PATIENTS WITH ASTHMA. PART 2: AIR POLLUTION, ANIMAL DANDER AND ASTHMA SYMPTOMS

JOHN H. KURATA, Ph.D., M. MICHAEL GLOVSKY, M.D., ROBERT L. NEWCOMB, Ph.D., and JAMES G. EASTON, M.D.

DURING THE LAST two decades interest in air pollution and its effects on diseases has been increasing. It is the belief of many that air pollution aggravates diseases of the upper and lower respiratory tracts, although this has not been established as fact. Specifically, in regards to patients with asthma, conclusions of previous studies indicate that air pollution may affect the severity of this condition. Zweiman et al,[1] in a review of studies on air pollution and asthma, concluded: " . . . it seems reasonable for physicians caring for asthmatic patients to be continually aware of the possibility that air pollution may be an aggravating factor . . . "

The major reasons that more definitive statements about the relevance of air pollution in asthma have not been made are as follows: (1) Most studies which have reported significant results did not classify patients with asthma separately from those with other obstructive bronchopulmonary diseases. Studies which specifically evaluated patients with asthma reported conflicting findings. (2) Most studies were epidemiologic and thus were confounded by the effects of meteorologic components, synergistic effects of other pollutants, pollens, etc.

In this study we are concerned with relationships between asthma and the four measurable air pollutants responsible for pulmonary irritations:[1,2,3,4] sulfur dioxide, oxidants (ozone), nitrogen oxides and carbon monoxide. We have included only patients who have been diagnosed as

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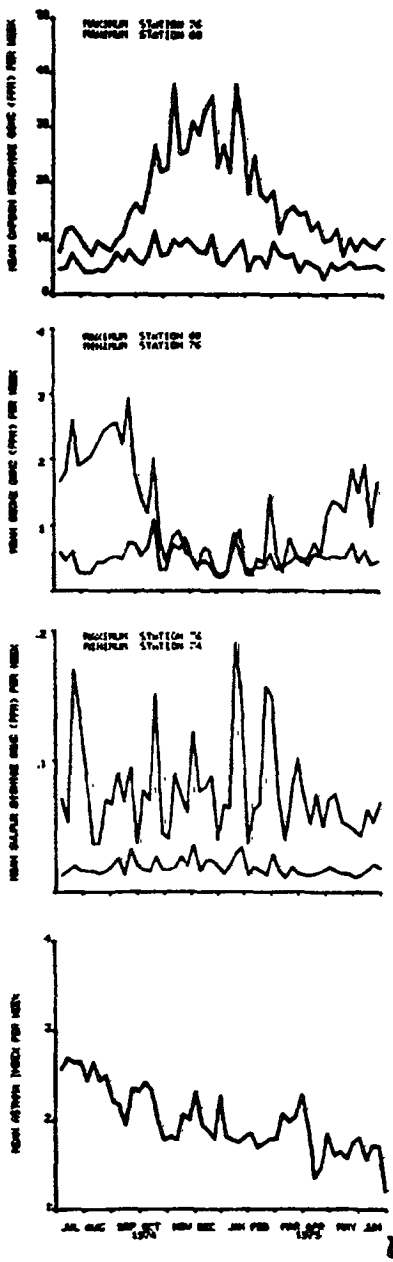
"asthmatic" by the standards described in Part I of this project[5] and thus have avoided the first problem listed above. We have avoided the second problem of failing to consider synergistic pollutant effects by collecting and analyzing data on several types of pollutants concurrently. Finally, in addition to the exposure to air pollutants, we present a preliminary multivariate analysis of concurrent exposure to animals. We will analyze other important factors such as concurrent exposure to pollens and psychological factors at a later date.

Materials and Methods

This section includes only a brief description of the materials and methods relevant to this study, since a more complete description can be found in Part 1.[5] All patients were diagnosed as having asthma on the basis of physical examinations, medical histories and response to bronchodilator medication. Most patients were on regular hyposensitization schedules based on histories and skin test reactivity. There were 20 males and 25 females, ranging from 7 to 72 years of age.

Patients recorded wheezing symptoms, medication for wheezing and other allergy related items daily on punch-card diaries for a period of one year. They mailed the diary cards back weekly and came to the allergy clinic for monthly interviews. Air pollution data from 13 air monitoring stations in the Los Angeles area were supplied by the Los Angeles Air Pollution Control District. The PDP-10 and Sigma-7



Figures 1–4. All graphs display weekly averages for the indicated variables for the common period from July, 1974, through June, 1975. The first three graphs contrast the stations reporting the maximum and minimum year-long concentrations. The last graph reports the average Asthma Index for all patients in the study.

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computers at the University of California, Irvine, were used to analyze the data.

*Asthma Index = (Day wheeze + Night wheeze + Medication for wheezing) The Formula for this index has been shortened to only three symptom variables. The range of values for this index is 0-9.

**The average concentration is based upon the mean of the daily instantaneous maxima for each station from July, 1974, to June, 1975.

Results

The weekly average of pollutants for all 13 stations and the weekly average of the Asthma Index* were plotted for July, 1974, through June, 1975. For the sake of brevity data from only the stations with the highest average concentrations and the stations with the lowest average concentrations** for each pollutant are pre-

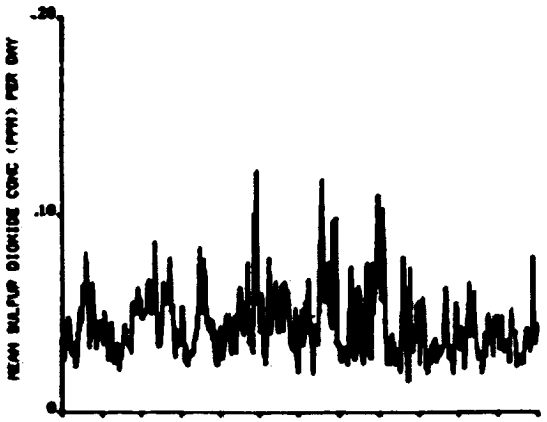

Figure 5. Mean sulfur dioxide concentrations in parts per million (PPM) per day for July, 1974, through June, 1975.

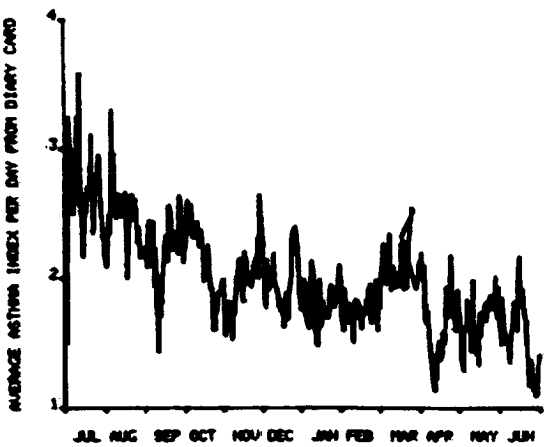

Figure 6. Mean Asthma Index per day for July, 1974, through June, 1975.

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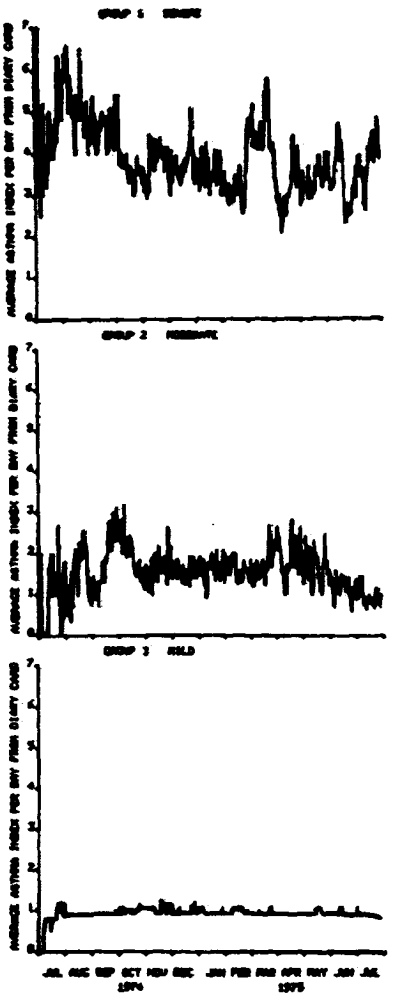
sented in Figures 1 through 3. A plot of the weekly average Asthma Index for all patients combined is presented in Figure 4. Visual examination of these figures does not reveal any marked or consistent relationships between pollutants and symptoms.

The severity of the air pollution levels presented in Figures 1-3 can be estimated by comparing these values with the California state air pollution standards for Stage 1 episodes.[6] Based on instantaneous maxima in parts per million (ppm): carbon monoxide = 50, sulfur dioxide = 3, ozone = 0.5, nitrogen oxides = 3. Based on one hour averaging times: carbon monoxide = 40, sulfur dioxide = 0.5, ozone = 0.2. During 1974 the following number of Stage 1 episode levels were attained in the Los Angeles basin: Carbon monoxide = 19, sulfur dioxide = 0, ozone = 84, nitrogen oxides = 6.

As a check to see whether the variance within each week would provide additional information, the daily averages of sulfur dioxide were plotted against their respective daily asthma index for the total patients (Figures 5-6). In addition we categorized the patients according to severity of symptoms and plotted the daily averages for these groups (Figures 7-9). We made this distinction since Carnow, et al[7] reported that 39 patients with severe bronchopulmonary disease over the age of 55 showed an increase in the acute morbidity rate in association with increased levels of sulfur dioxide. Visual examination of these plots also does not reveal any noticeable relationships. After plotting these single variables over time, a more controlled and quantitative evaluation of the data was made by matching each individual's daily Asthma Index with the daily pollution level in his/her residential zone.

Figures 10-12 illustrate the relationship between the average Asthma Index for all patients and the corresponding categorized pollution levels. Level of exposure was defined



Figures 7-9. Mean Asthma Index per day for patients grouped according to severity of symptoms. Note that the scale has been changed from the previous figures in order to accommodate the larger range of values

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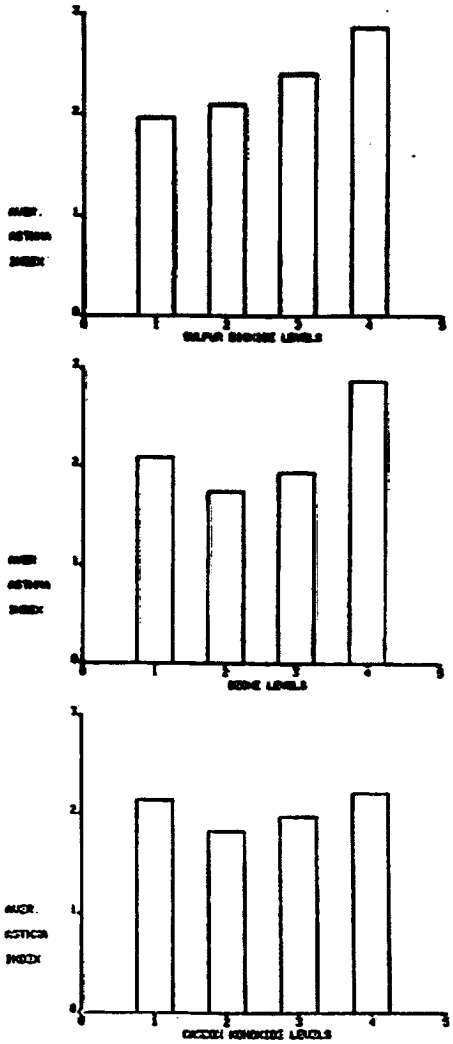

Figures 10-12. All graphs display averages of the Asthma Index scores grouped according to exposure to four levels of air pollutant concentrations (PPM). (July, 1974, to July, 1975)

Sulfur Dioxide: Level 1: .01, .02, .03, .04, .05
Level 2: .06, .07, .08, .09, .10
Level 3: .11, .12, .13, .14, .15
Level 4: .16, .17, .20, .26, .30

Ozone: Level 1: .01 - .09
Level 2: .10 - .18
Level 3: .19 - .27
Level 4: .28 - .37

Carbon Monoxide: Level 1: 1 - 11
Level 2: 12 - 22
Level 3: 23 - 33
Level 4: 34 - 56

as the daily air pollution reading (range) in the air monitoring zone where the patient resides. Data for days on which patients reported that they were out of town were excluded. These graphs appear to show a positive relationship between sulfur dioxide and ozone levels and the Asthma Index. However, these bar graphs are misleading since they do not take into account the variance and number of reports which comprise each level of pollutants.

As can be seen from Table I, one major problem with making conclusions based solely upon these bar graphs is that the number of reports which comprise each pollutant level varies. For example, the number of reports which correspond to pollution levels of 32 ppm, 34 ppm and 37 ppm of ozone is only 2, 2 and 1 respectively. Thus the three highest Asthma Index means (5.5, 6.5 and 5.0) make the average value for the Level 4 group high even though they reflect only a small percentage of the scores reported by that group. Furthermore, not only did these five reports come from only two patients but neither of these patients reported more asthma symptoms with increasing ozone concentrations. Pearson's correlation coefficient, which takes into account this variability, was less than .10 between each pollutant and the Asthma Index. In summary, then, if we had neglected to take into account the sample size and variance for each subgroup, we might have erroneously reported a positive relationship between exposure to increasing concentrations of ozone and an increase in asthma symptoms.

Table II illustrates that air monitoring zones may be high in one pollutant and very low in another. This makes it inappropriate in our study to evaluate the long-term effect of pollutants by

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TABLE I. MEAN ASTHMA INDEX PER OZONE LEVEL BY GROUPS EXPOSED TO FOUR LEVELS OF OZONE CONCENTRATIONS.

	Ozone Level In PPM	Mean Asthma Index	Number of Reports
Level 1	.01	2.850	307
	.02	2.374	981
	.03	2.166	1401
	.04	2.058	1252
	.05	1.956	1104
	.06	2.058	791
	.07	1.842	822
	.08	1.978	712
	.09	1.822	443
Level 2	.10	1.601	489
	.11	1.854	424
	.12	1.671	426
	.13	1.779	335
	.14	1.634	372
	.15	2.082	243
	.16	1.898	196
	.17	1.956	183
	.18	1.554	242
Level 3	.19	1.581	105
	.20	1.802	131
	.21	1.869	99
	.22	1.913	115
	.23	1.912	80
	.24	2.135	96
	.25	2.364	33
	.26	2.241	54
	.27	2.414	29
Level 4	.28	2.162	37
	.29	2.850	20
	.30	2.600	20
	.31	1.250	20
	.32	5.500	2
	.33	2.385	26
	.34	6.500	2
	.36	1.571	7
	.37	5.000	1

TABLE II. RANK ORDER OF AIR MONITORING STATIONS ACCORDING TO AVERAGE CONCENTRATION OF POLLUTANTS.

	Sulfur Dioxide		Ozone		Carbon Monoxide		Nitrogen Oxides		Particulates	
Station	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank
1	.043	2	.097	5	14.2	1(H)	.420	1(H)	97	3
60	.032	5	.119	1(H)	6.4	7(L)	.213	7(L)	106	1(H)
69	.036	4	.103	3	13.3	2	.353	2	No Data	
71	.038	3	.068	6	9.5	6	.339	3	106	1(H)
74	.019	7(L)	.102	4	9.6	5	.328	5	84	5
83	.032	5	.116	2	12.4	4	.333	4	80	6(L)
84	.055	1(H)	.045	7(L)	13.2	3	.275	6	87	4

* Average of the Daily Instantaneous Maxima (In PPM) for July 1974–July 1975.
(L) =Station with lowest average concentration.
(H) =Station with highest average concentration.

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categorizing residential zones into high and low zones since the sample size within each zone is not large enough to take into account the inverse relationships between these pollutants. In addition, Figures 1-3 show that the different pollutants reach peak concentrations during different seasons of the year.* Thus, since the total group of patients displays symptoms consistently year round, we cannot explain much of the variance in symptom patterns by relating symptoms to only one kind of pollutant. However, even when we used multivariate data analysis techniques, we still could not show significant relationships between these three pollutants and asthma symptoms. Tables III and V show the results of a step-wise multiple regression analysis[6] which we used as a means to construct a linear combination of independent variables which best predicts the dependent variable (Asthma Index). Four measurements are presented for each independent variable. The multiple R is the correlation between the dependent variable and the independent variable from the current and preceding steps. The simple R is the correlation between the independent and dependent variables. The B is the regression coefficient and the BETA is the normalized regression coefficient.

In addition we have done some preliminary analyses of animal exposure concurrently with the air pollution factors. Table IV shows the results of a test of the difference between severity of asthma symptoms (Asthma Index means) for the patients who did not own cats and dogs and those who owned cats and dogs (indoors and outdoors). The results of the data for the first six months (described in Part 1 of this series) and for the whole year (Table IV) show that patients who owned cats and dogs reported a significantly higher mean Asthma Index. This consistency between the data from the first six months and the whole year strengthens the hypothesis that constant exposure to these animals is related to the greater severity of their symptoms. As a means of measuring which variables are most strongly related to the Asthma Index, we performed the step-wise multiple regression analysis again (Table V), this time adding animal exposure to our list of independent variables. Results of these analyses indicate that a much greater percentage of the variance of the asthma symptoms can be accounted for by exposure to animals than to air pollutants.

Discussion

Previous studies on air pollution and asthma have produced conflicting results. Table VI illustrates some of

*The different characteristics of these pollutants (Figures 1-4 and Table I) can be explained by the fact that ozone is a "secondary" pollutant, whereas oxides of nitrogen and carbon monoxide are "primary" pollutants. Primary pollutants reach their peak right after emission, while secondary pollutants are by-products of reactions (e.g., photochemical) and reach their peak later in the day when they might have been carried by winds into a different zone. Also, "the highest average concentrations of ozone are measured during the months of June through October, when horizontal and vertical dispersion of auto emissions are limited and optimum sunshine is available."[6]

TABLE III. STEP-WISE MULTIPLE REGRESSION WITH THE ASTHMA INDEX AS THE DEPENDENT VARIABLE AND CARBON MONOXIDE, OZONE AND SULFUR DIOXIDE AS THE INDEPENDENT VARIABLES.

	MULTIPLE R	SIMPLE R	B	BETA
Carbon Monoxide	0.04809	-0.04809	-0.00505	-0.05374
Ozone	0.06996	-0.04652	-0.00484	-0.03852
Sulfur Dioxide	0.09034	0.03038	0.01872	0.06203

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these results according to their respective research designs.

As can be seen from this table, Zeidberg et al[15] reported significant associations between ambient sulfur dioxide levels and asthma symptoms. They reported that ". . . when the attack rates on the thirty days of the highest SO_2 levels were compared with the rates on the forty-six days with the lowest levels, the difference in the respective rates of 0.130 and 0.110 was significant at the 5% level."[15] Two important points should be noted. First, the attack rate of 0.130 on days of high sulfation was lower than the average attack rate (0.133) for all days, irrespective of

TABLE IV. TEST OF DIFFERENCES BETWEEN RECODED ASTHMA INDEX MEANS FOR DATA FROM JULY, 1974 - JUNE, 1975.

	Mean Score of the Recoded Asthma Index or Each Patient Grouped According to Exposure to Animals		
	(1) No Animals	(2) Animals Inside the Home	(3) Animals Outside the Home
	0.125	0.520	3.448
	0.348	1.745	3.799
	0.137	5.869	2.382
	0.044	4.880	0.429
	1.976	0.962	1.946
	1.454	0.317	3.612
	0.157	6.350	0.475
	0.042	3.650	5.630
	4.104	4.627	5.543
	1.878	4.058	3.398
	0.035		5.623
	3.368		3.599
	1.154		
	1.137		
	0.308		
	0.248		
	0.148		
	2.298		
	0.905		
	3.015		
	1.470		
Mean	1.160	3.298	3.324
Std. Dev.	1.221	2.245	1.789
N	21	10	12

*$t_{1,2} = 3.455$ ($p < .005$)
*$t_{1,3} = 4.128$ ($p < .005$)
$t_{2,3} = 0.030$ ($p > .05$)

TABLE V. STEP-WISE MULTIPLE REGRESSION WITH THE ASTHMA INDEX AS THE DEPENDENT VARIABLE AND CARBON MONOXIDE, OZONE, SULFUR DIOXIDE, AND ANIMAL OWNERSHIP AS THE INDEPENDENT VARIABLES.

	Multiple R	Simple R	B	Beta
Carbon Monoxide	0.04809	-0.04809	-0.00505	0.05374
Ozone	0.06996	-0.04652	-0.00484	-0.03852
Sulfur Dioxide	0.09034	0.03038	0.01872	0.06203
Animal Owners	0.37832	0.37150	0.57197	0.36841

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SO_2 levels. Second, a check of the graph (Figure 5, from Zeidberg, 1961) shows that the two peaks (maximum attack rates) for asthma attacks occur in October and May when SO_2 is near its minimum levels. From these observations it is difficult to accept that the difference between mean attack rates of 0.130 and 0.110 could be very meaningful. It would have been most helpful if standard deviations or at least the statistical tests used to verify

TABLE VI. SUMMARY OF PREVIOUS STUDIES ON EFFECTS OF AIR POLLUTION ON ASTHMA.

			Independent Variables					
Dependent Variable	Mode of Analysis	Investigator	CO	SO_2	Oxidants	Particulates	Dust	Poor Combustion Particle with Associated Silica
Visits to hospital for asthma	Day-by day association	Ribon, et al.[4]	-	-	-			
		Greenburg, et al.[9]	-	-				
		Goldstein, et al.[10]		(-+)				
		Lewis, et al.[11]						+
		Girsh, et al.[12]	±(?)	+(?)	+(?)	+(?)	+(?)	
	Frequency by residential zones	Sultz, et al.[13]				+		
	Day-by-day association	Schoettlin, et al.[14]						
Asthma symptoms via daily diary	Day-by-day association & frequency by residential zones	Zeidberg, et al.[15]		+				

\- = Reported no significant associations
\+ = Reported significant association
+(?) = Girsh, et al. "Could not incriminate any Specific pollutants."
(-+) = Goldstein, et al. found small, negative (partial) correlations in Harlem; but found strong positive (partial) correlations in Brooklyn. Since levels of sulfur dioxide were higher on the average in the Harlem area than in the Brooklyn area, they concluded: ". . we feel that in our case SO_2 is not necessarily the causative agent, but might rather implicate some other confounding variable . . ."

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significance at the .05 level had been stated.*

Schoettlin and Landau[14] were the only investigators to report finding significant associations between ozone levels and asthma symptoms. They concluded from their study, which went from September through December of 1956, that a "significantly greater number of persons had attacks on days with high enough oxidant values to cause eye irritation (25 ppm) than on other days . . ." They did not provide in their report values for the means, number of people reporting each day and type of statistical test used. They also did not report whether the "25 ppm" criteria was based on instantaneous maxima or one-hour averaging times. This is especially important since, through correspondence with the Los Angeles Air Pollution Control District, we know that there were only five days during which 25 ppm was exceeded based on the one-hour averaging time, and 11 days based on the instantaneous maxima criterion. Thus at the best, 11 days were compared with 87 days and, at the worst, 5 days were compared with 93 days. It is also important to know that there were only three days in September and two days in October when ozone exceeded 25 ppm, based on the one-hour averaging time; while only seven days in September and four days in October exceeded this level based upon instantaneous maxima. Thus, since there were no "high oxidant" days in November and December, the data for the high versus low oxidant groups were sampled over different times of the year when other seasonal factors may have influenced the results. An even more important point is that the mean for each group should be based upon the proportion of persons reporting attacks (# of attacks/# of people reporting) per day. For example, since the number of persons reporting each day was not given, there may have been fewer persons reporting by November when there were no days on which ozone exceeded the criterion level. Thus this significant result, using the mean number of reported attacks, could actually be due to fewer persons turning in reports during the last month of the three-month study.

A major reason for our critique of the Zeidberg and Schoettlin articles is to clear up some of the confusion in the literature pertaining to effects of air pollution and asthma. Part of this confusion stems from authors who have cited the conclusions of these two studies without discussing any of the problems in the data analysis procedures and some who also have made erroneous statements about the results. For example, other authors who have cited the Schoettlin and/or Zeidberg studies as evidence for a relationship between air pollutants and asthma include Zweiman et al,[1] Girsh et al,[12] Lave et al,[17] Chiaramonte et al[18] and Salvaggio et al.[19].

Conclusion

In the preceding discussion we have shown not only that our own data do not indicate a strong association between air pollution and asthma but also that the two other studies which used daily diaries to measure asthma symptoms did not show convincing evidence either. In fact our data, combined with the studies listed in Table VI, indicate that at least as many epidemiological studies have found negative results as positive results.

In addition to the epidemiological studies by Ribon,[4] Greenburg,[9] and Goldstein,[10] recent laboratory investigations compare favorably with our results. For example, even though

*For a more detailed critique of this study see dissertation manuscript.[16]

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Hackney et al included volunteers with a history of "hyper-reactive" airways in their study, they reported "no-detectable-effects" on pulmonary function tests and symptomatology at levels of 0.25 to 0.30 ppm of ozone.[20,21] However they found significant effects at 0.37 ppm of ozone. Our patients had only one exposure to a level as high as 0.37 ppm and, therefore, were probably not exposed to the ozone concentrations needed to produce noticeable effects.

This inability to show positive relationships, however, does not mean that these relationships do not exist. Factors which may have influenced our results include the following.

(1) The study of air pollutants is complicated by the fact that more than one pollutant may be important in asthma and peak concentrations of these different pollutants are often inversely related in terms of both residential zones and time of the year. For example, patients in a study may be classified as residing in the highest sulfur dioxide zone and at the same time unknowingly be in the lowest oxidant zone. Future studies should ensure that enough patients live in each residential area to adequately analyze the effect of these different pollutants.

(2) Patients may have adapted behaviorally and physiologically to the air pollutants. Behaviorally, patients may be staying indoors and reducing their participation in strenuous activities on smoggy days. Physiologically, recent studies[22] have indicated that Los Angeles residents may build up a tolerance to ozone. Also, D.L. Dungworth et al[23,24] have reported that although there is damage to the lungs of monkeys which were exposed to ozone concentrations greater than 0.5 ppm, the damage lessens when the exposure is below 0.5 ppm and disappears when the exposure is below 0.2 ppm. Since none of our patients were exposed to ozone concentrations greater than 0.37 ppm, this repair and adaptation which occurs below 0.5 ppm may be a reason why we did not detect any significant relationships between ozone concentrations and asthma symptoms.

(3) Patients selected for this study have been undergoing hyposensitization. Although this may have affected the frequency and severity of asthma symptoms, it was necessary to use these patients in order to ensure that our patients would be seen regularly.

(4) Patients may have been inaccurate in reporting their symptoms. We reduced the importance of this factor as much as possible by interviewing the patients at least once a month and collecting their reports weekly. In addition the consistency between our data and that from other studies reduces the likelihood that inaccuracy of reporting was a major problem.

(5) Particulates or other air pollutants may be more important than the pollutants that we studied.

(6) The subjects in our study may not have been exposed to the threshold levels of air pollutants required to detect their effects. Thus there is a strong possibility we did not find significant associations because other factors such as exposure to animals had greater immediate consequences than exposure to ambient levels of air pollutants.

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